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Case Report

Management of erythropoietic protoporphyria with cholestatic liver disease: A case report

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ABSTRACT

Erythropoietic protoporphyria (EPP) is a rare metabolic disease of the heme biosynthetic pathway where an enzymatic dysfunction results in protoporphyrin IX (PPIX) accumulation in erythroid cells. The porphyrins are photo-reactive and are responsible for severe photosensitivity in patients, thus drastically decreasing their quality of life. The liver eliminates PPIX and as such, the main and rare complication of EPP is progressive cholestatic liver disease, which can lead to liver failure. The management of this complication is challenging, as it often requires a combination of approaches to promote PPIX elimination and suppress the patient's erythropoiesis. Here we described a 3-year follow-up of an EPP patient, with three episodes of liver involvement, aggravated by the coexistence of a factor VII deficiency. It covers all the different types of intervention available for the management of liver disease, right through to successful allogeneic hematopoietic stem cell transplantation.

1. Introduction

Erythropoietic protoporphyria (EPP) is an inherited metabolic disease caused by a reduced activity of the last enzyme of the heme biosynthesis pathway, ferrochelatase (FECH) [1]. FECH catalyzes the insertion of iron into protoporphyrin IX (PPIX) to form heme. FECH partial deficiency leads to metal free PPIX accumulation in erythroid cells, leading to phototoxic reactions responsible for long lasting painful photodermatosis after sun exposure. Thus, EPP patients have a markedly reduced quality of life. PPIX is a hydrophobic compound strictly eliminated by the liver. In a small subset of patients, around 5%, hepatic accumulation of PPIX is responsible for a progressive liver disease that could lead to liver failure [2,3]. Here we describe a case of EPP hepatopathy associated with factor VII deficiency responsible for repetead blood loss and chronic stimulation of the patient's hematopoiesis contributing to PPIX accumulation.

2. Case report

A 40-year-old woman with EPP diagnosed at the age of 5 presented 3 episodes of liver involvement between the year 2018 and 2021. (Fig. 1A). Written informed consent has been obtained from the patient to publish this paper. All procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000. The diagnosis was confirmed biochemically, with a baseline erythrocyte porphyrins level of 80–100 μmol/L erythrocytes ($N < 1.9$, Zinc protoporphyrin 6% or

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less) and decreased ferrochelatase activity. Analysis of the *FECH* gene revealed a complete gene deletion in trans of the c.315-48 T > C hypomorphic variant. She had no other medical history except for factor VII deficiency (17%) which was responsible for recurrent epistaxis. Liver tests and liver imaging revealed no other cause of liver disease apart from moderate steatosis: hepatitis B, C and E were excluded, and no gallstones or biliary tract dilatation were observed. The patient did not consume alcohol. Deficit in alpha-1 antitrypsin and Wilson's disease were not investigated. Firstly, in November 2018, she presented with jaundice following oral iron supplementation. Her general practitioner

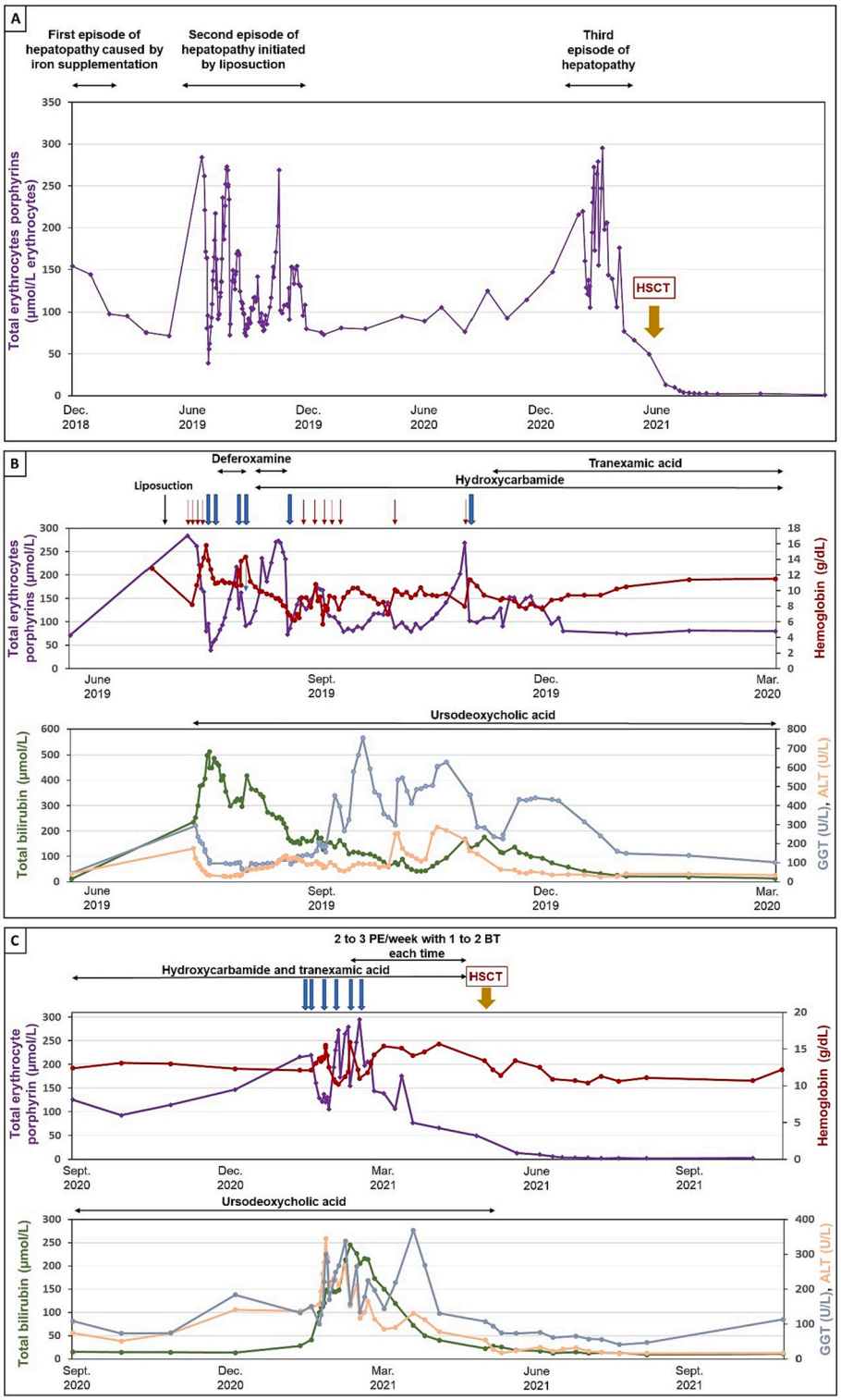

Fig. 1. Patient biological parameters throughout the three episodes of EPP-related hepatopathy.
A: erythrocyte total porphyrins level during the three episodes of liver involvement. B (second episode) and C (third episode): upper panel, total erythrocyte porphyrin level (purple diamonds) and hemoglobin level (red dots), lower panel: total bilirubin (green), ALT (orange) and GGT (blue, only in panel B) levels. Small red arrows indicate blood transfusions. Large blue arrows indicate red blood cells exchange. HSCT: hematopoietic stem cell transplantation; PE: plasma exchange; BT: red blood cells transfusion.

introduced oral iron therapy because of fatigue associated with microcytic anemia and low ferritin levels, often seen in patients with EPP, and probably aggravated by repeated bleedings. Liver function tests (LFTs) performed at that time showed increased AST (200 U/L, $N < 37$) and ALT (226 U/L, $N < 59$) with increased bilirubin and without cholestasis (total bilirubin up to 67 μmol/L, $N < 17$, conjugated bilirubin 57 μmol/L, alkaline phosphatase ALP 99 U/L, $N < 135$). Her erythrocyte total porphyrins level was 154 μmol/L erythrocytes ($N < 1.9$, last known value was 104 μmol/L in 2012). Iron discontinuation and ursodeoxycholic acid (UDCA, 500 mg orally twice daily) administration led to complete normalization of hepatic function after five months and a half. Meanwhile, erythrocytes porphyrins decreased by >50%, to 71 μmol/L.

Secondly, seven months later, in June 2019, the patient underwent a liposuction, which was complicated by a significant blood loss: her hemoglobin (Hb) level decreased from 12.8 g/dL to 8.2 g/dL after the procedure. This was presumably responsible for an important stimulation of her erythropoiesis and resulted in massive accumulation of PPIX. Indeed, her erythrocytes porphyrins level increased to 284 μmol/L and her reticulocyte count reached 226 G/L (N 50–120). The rise in PPIX level was accompanied by severe cholestasis (bilirubin level up to 513 μmol/L and GGT 295 U/L, $N < 55$ and ALP 375 U/L, Fig. 1B). Several interventions were performed to increase the patient's hemoglobin level and promote a decrease in PPIX levels. First, 4 transfusions of packed red blood cells were performed to treat the anemia (Fig. 1B). To further inhibit endogenous erythropoiesis and remove PPIX from the patient's red blood cells, 5 sessions of red blood cells exchange were performed. UDCA (500 mg orally twice daily) was introduced to promote hepatic elimination of PPIX. Red blood cells exchange was the only treatment inducing a short term decrease in erythrocytes porphyrins level. Deferoxamine was introduced twice in an attempt to decrease iron store and thus slow down hematopoiesis, but thrombocytopenia occurred each time and was considered as an adverse effect. At first, the patient was treated with IV deferoxamine for 14 days at a dose of 20 to 60 mg/kg/day until thrombocytopenia occurred (nadir platelet count 24 G/L), 5 days later it was then resumed at a dose of 20 mg/kg/day for 10 days which was accompanied by a novel episode of thrombocytopenia. Instead, hydroxycarbamide (1000 mg per day, orally)was started to achieve this objective. During hospitalization, several episodes of posterior epistaxis occurred, requiring nasal packing and red blood cells transfusions. In July, August and September 2019, the patient presented several episodes of melena with posterior epistaxis associated with severe decrease in Hb level that required her transfer to an intensive care unit and red blood cells transfusions. Anemia was responsible for erythropoiesis stimulation that contributed to PPIX accumulation. To control epistaxis, tranexamic acid (3 g per day, orally) was introduced in November 2019. Under treatment, bleeding episodes were less frequent. Reticulocyte counts decreased to the lower limit of the normal range, between 50 and 70 G/L and remained stable from December 2019 to February 2021. As of December 2019, erythrocytes porphyrins levels returned to their initial value, around 80 μmol/L and remained stable until March 2020. LFTs progressively returned to normal values, 9 months after the surgical procedure that resulted in PPIX accumulation, except for GGTs that remained around two times the ULN.

Finally, in February 2021, 26 months after the initial episode and without any triggering factor identified, the patient showed further deterioration of her liver function despite hydroxycarbamide, tranexamic acid and UDCA treatment (Fig. 1C). During this episode, bilirubin level reached 245 μmol/L, ALT level 345 U/L and erythrocytes porphyrins was up to 295 μmol/L. In view of this third episode of EPP-related hepatopathy and the risk of recurrence, hematopoietic stem cell transplantation (HSCT) indication was established. To evaluate the hepatic damage caused by repeated episodes of cholestasis and the liver ability to endure a busulfan treatment, a liver biopsy was performed. It showed preserved parenchymal architecture with portal and sinusoidal fibrosis, but without complete septa, discrete steatosis as well as pigments typical of PPIX deposition (Fig. 2). In the absence of extensive fibrosis, the patient was referred for allogeneic HSCT without liver transplant. Iterative red blood cells exchange and plasma exchange, associated with blood transfusions, were able to normalize the liver function and erythrocytes porphyrins decreased to 50 μmol/L. A HSCT was then successfully performed in May 2021, 30 months after the initial episode of EPP-related hepatopathy. By the end of July 2021, the patient erythrocytes porphyrins level was in the normal range. She did not present with any photosensibility and she was then able to expose herself to sunlight during daytime without any restriction to date (May 2023).

3. Discussion

This case highlights the several treatments available in EPP patients with liver disease. A first approach might be to use treatments to promote PPIX liver elimination, mostly UDCA [4]. Red blood cells exchange and plasmapheresis are two other means of reducing circulating PPIX (it should be noted that plasmapheresis is theoretically less efficient in removing PPIX as PPIX concentrations in plasma are in nmol/L whereas it is in μmol/L in erythrocytes) [5]. Red blood cells exchange is used to maintain Hb level and to suppress the patient erythropoiesis. To slow down the patient erythropoiesis, another treatment option is to induce iron deficiency. This strategy was used with success in congenital erythropoietic porphyria patients to reduce the porphyrins accumulation and there are reports of its use in EPP-related hepatopathy [6–9]. This could be achieved by two means: iron chelators or iterative phlebotomies. However, iron deficiency could take a long time to achieve depending on the initial ferritin level, especially if the patient was transfused several times. Furthermore, iron chelators toxicity should be considered, especially in context of hepatopathy. Moreover, the

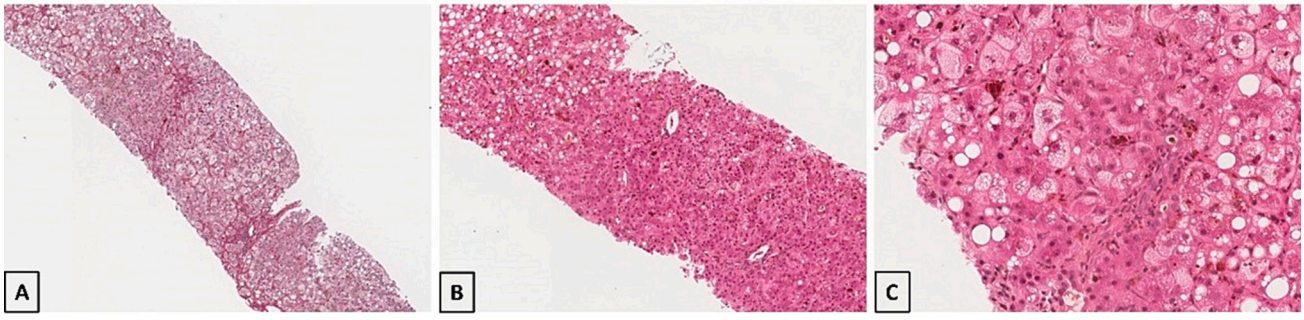

Fig. 2. Liver biopsy.
A: sirius red stain showing preserved lobular architecture with mild portal fibrosis and perisinusoidal fibrosis (x10). B: liver parenchyma showing mild steatosis and regenerative hepatocellular areas with brown pigment accumulation (hematein & eosin stain x20). C: brown pigment accumulation is observed in bile canaliculi and in Kupffer cells with sinusoids; some hepatocytes are steatotic (macro- and microvesicular steatosis, hematein & eosin stain x40).

induction of iron deficiency is not a suitable strategy for rapid erythropoiesis inhibition. Hydroxycarbamide, in combination with blood transfusions, induced a biological and a clinical improvement in a patient with delta-aminolevulinic acid dehydratase-porphyria [10]. In our case, the patient's hematopoiesis was stimulated by iron supplementation, surgery and recurrent blood loss due to subsequent episodes of epistaxis. Attempts to slow it down by inducing martial deficiency failed due to the occurrence of a rare adverse event, which prompted us to discontinue iron chelation therapy. The only treatment associated with a swift reduction of erythrocytes PPIX level was red blood cells exchange. The combination of tranexamic acid, to prevent bleeding, and hydroxycarbamide, to slow down hematopoiesis, was associated with a slow-down in erythropoiesis. The use of hydroxycarbamide enabled us to slow down the patient's erythropoiesis without depleting iron stores and without excessively inhibiting the production of other lineages. This report underlines the fact that those treatments should be used in combination to promote PPIX elimination and hematopoiesis inhibition. It is still unclear how iron metabolism interacts with EPP physiopathology as there are conflicting reports regarding the effect of iron oral therapy in patients [11–16]. However, recent reviews concluded that available data suggest that iron could worsen EPP symptoms [17,18]. Thus, EPP patients should be warned about iron oral therapy that should be initiated only if responsible of clinical symptoms and under close monitoring of LFTs and porphyrins level. It should be noted that in the rarer form of EPP, caused by a gain of function variant in ALAS2, the first enzyme of the heme biosynthesis pathway, iron oral therapy seems beneficial [19].

Several cases of liver transplant were reported in EPP patients [4,20–22]. Frequency of recurrent liver disease on the transplant was reported to be as high as 80%. Thus, sequential liver transplantation and allogeneic HSCT should be considered to avoid a repeat liver transplantation. Ideally, HSCT should be performed as early as possible, prior to EPP-cirrhosis, to avoid a liver transplantation.

Further studies are needed to identify individuals at risk for EPP-related hepatopathy as only a small percentage of patients are presenting with progressive liver disease. In the meantime, LFTs and erythrocytes porphyrins level of EPP patients should be monitored at least once a year.

Authorship

A.P. and L.G. wrote the manuscript. A.P., N.T., C.F., J.D., M.S., N.P., E.A., F.S.F. and L.G. followed the patient clinical course. A.M., C.S., T.L., B.M. and H.P. performed the biochemistry studies. V.P. performed the pathological study. All authors analyzed the data and edited the manuscript.

Declaration of Competing Interest

The authors declare no competing financial interests.

Data availability

Data will be made available on request.

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